27. (New) The transgenic see-though medaka according to claim 23 wherein said organ is a gonadal organ.

28. (New) The transgenic see-through medaka according to claim 24 wherein said organ is a gonadal organ.

B2 cont

29. (New) The transgenic see-through medaka according to claim 25 wherein said organ is a gonadal organ.

30. (New) The transgenic see-through medaka according to claim 26 wherein said organ is a gonadal organ.

REMARKS

Claims 1 to 22 were pending. Applicants have amended claims 7-22, as set forth in the attached appendix, and added claims 23-30. The amendments and the new claims are supported by the specification and the originally filed claims. Specifically, claims 7-22 now recite a transgenic see-through medaka, as is supported at page 10, lines 7 and 26, and page 30, line 5 of the specification. Also, the specification at page 5, lines 2-6; page 9, lines 15-20; and page 11, lines 22-24, describe support for the characteristics of the medaka of claims 23 and 24. The specification at page 5, lines 7-9, support the green fluorescent element of new claims 25 and 26. And, finally, the specification at page 5, lines 10-11, support the gonadal organ aspect of claims 27-30. Thus, there is no issue of new matter. With the entry of this amendment, claims 1-30 are now pending.

Entry of July 16, 2001 Amendment

Applicants wish to thank the Examiner for entering the amendment filed on July 16, 2001 with respect to claim 6.

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Claim Rejections Under 35 U.S.C. § 112, First Paragraph

The Office rejected claims 1-22 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification. Office Action at page 2. Applicants respectfully traverse these rejections.

First, the Office contended that the invention did not satisfy the "how to make" requirement without a biological deposit, because the see-through medaka are produced "by a method that is not readily reproducible." Office Action at page 2. According to the Office, producing the medaka of the instant invention by repeated selective mating is not "exactly reproducible . . . so that the genetic make up of the organism differs with each trial of mating." *Id.* The Office thus concluded that a biological deposit was needed for enablement. Office Action at pages 2-3.

The Office bears the initial burden to establish that access to a biological material is necessary to satisfy 35 U.S.C. § 112. M.P.E.P. § 2411; 37 C.F.R. § 1.809. Applicants submit that this burden has not been met and that a deposit is not required under the circumstances of the instant application.

Applicants respectfully remind the Office that exact reproducibility of claimed organisms is not required to satisfy § 112, first paragraph. A very recent opinion from the U.S. Patent and Trademark Office Board of Patent Appeals and Interferences, *Ex parte Chen*, 61 U.S.P.Q.2d 1025 (Bd. Pat. App. & Interf. 2000), directly addressed this issue in reversing a final rejection of claims to a transgenic carp. According to the examiner in that case, the specification did not disclose a process that was "repeatable" as to the levels of expression of the transgene product in the claimed fish. *Id.* at 1028. However, the Board explained that "[t]he examiner's concerns relating to ... *reproducibility of identical fish are misplaced,* because the claims do not include or require these

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limitations." *Id.* (Emphasis added). The Board thus reversed the examiner's rejections under 35 U.S.C. § 112, first paragraph. *Id.* at 1029.

Analogously, here, the Office's concern as to whether the method for producing the see-through medaka is "exactly reproducible" is misplaced because the pending claims do not include or require the genetic make-up of the medaka to be the same. Indeed, the claim recites only phenotypic characteristics, that is, that the medaka be see-through and that they be deficient in iridophores, melanophores, xanthophores and leucophores. Thus, the Office has not established a lack of enablement under 35 U.S.C. § 112, first paragraph. Accordingly, it cannot establish the necessity of a biological deposit in accordance with the Office's initial burden.

Moreover, no deposit is necessary where "the required biological materials can be obtained from publicly available material with only routine experimentation and a reliable screening test." M.P.E.P. § 2402.02. *Tabuchi v. Nubel*, 559 F.2d 1183, 194 U.S.P.Q. 521 (C.C.P.A. 1977); see also 37 C.F.R. § 1.802(b) ("Biological material need not be deposited, *inter alia*, if it is known and readily available to the public or can be made or isolated without undue experimentation.").

In the instant application, the medaka strains required as starting materials to make the claimed invention are known and readily available. Indeed, because medaka is widely used as a simple and useful experimental animal, those in the field are very familiar with it. Specification at page 2. In fact, many of these strains are well-known, having been studied and collected since the 1970's. See, for example, Specification at page 13, Table 1. Indeed, the Office recognized the availability of color mutants. *See*, Office Action at pages 8-9, reciting Ozato *et al.*, which discloses that "49 color mutants of medaka are maintained and available at the Nagoya University ... ." Moreover, as the

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specification discloses, medaka strains that can be used for the selective matings are obtainable from the Bioscience Center of Nagoya University and from the Department of Integrated Biosciences, Graduate School of Frontier Sciences, University of Tokyo. Specification at page 7, lines 1-6 and page 8, lines 17-26. Thus, one of skill in the art could readily obtain the biological starting materials needed to make the invention of the instant application.

Further, the screening test for identifying the medaka of the claimed invention simply involves observing the see-through phenotype and selecting the medaka that appear clearest. As noted in the specification, the progeny of each selective mating reach sexual maturity in just two months (Specification at page 2), and the resulting claimed medaka are plainly "see-though." Thus, the involved biological materials can be obtained by a simple and reliable screening test.

For at least the above reasons, Applicants earnestly and respectfully request reconsideration and withdrawal of the request for a biological deposit.

Second, the Office rejected claims 1-3 and 4-6 as allegedly not being completely enabled by the specification. Office Action at pages 4 and 7. According to the Office, the breath of claims 1-3 and 4-6 surpassed that of the specification. Office Action at pages 6 and 9.

As an initial matter, however, Applicants respectfully point out that the Office in fact concedes enablement with respect to claims 2, 3 and 5. Office Action at pages 4, 6, 7 and 9. Specifically, the Office describes the specification as "being enabling for a see-through medaka which is deficient in iridophores, melanophores, xanthophores and leucophores, wherein said deficiency is a result of repeated mating between iridophore deficient mutant mekaka strain 'gu', albino mutant medaka strain 'i-3' and leucophore

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deficient mutant medaka strain 'lf' and further selective mating between the resulting medaka and iridophore deficient mutant medaka strain 'il-1' ... ." *Id.* at page 4. Further, the Office recognizes that "[t]he specification and the working examples provide sufficient guidance to practice the invention with ... a see-through medaka which in deficient in iridophores, melanophores, xanthophores and leucophores, wherein the said deficiency is a result of repeated mating between iridophore deficient mutant medaka strain 'gu', albino mutant medaka strain 'i-3' and leucophore deficient mutant medaka striant 'lf' and further selective mating between the resulting medaka and iridophore deficient mutant medaka strain 'il-1' ... ." *Id.* at page 6 (emphasis added). Because the language of these two phrases almost exactly parallels the language of claims 2 and 3, the Office has acknowledged that the specification is enabling with respect to claims 2 and 3.

Similarly, the Office describes the specification as "being enabling for a see-through medaka which is deficient in iridophores, melanophores, [and] xanthophores, wherein the said deficiency is a result of repeated mating between iridophore deficient mutant medaka strain 'gu', albino mutant medaka strain '[i]-3' and leucophone deficient mutant medaka strain 'lf' and mekaka FLF strain which is deficient in leucophores in the female, and thereby allowing the identification of the sex of said medaka by the presence or absence of leucophores and/or a DNA marker, SL1 ... ." Office Action at page 7. And again, the Office recognizes that "[t]he specification and the working examples provide sufficient guidance to practice the invention with ... a see-through medaka which is deficient in iridophores, melanophores, [and] xanthophores, wherein the said deficiency is a result of repeated mating between iridophore deficient mutant medaka strain 'gu', albino mutant medaka strain 'i-3' and leucophore deficient mutant medaka strain 'lf' and medaka FLF strain which is deficient in leucophores in the female, and thereby allowing

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the identification of the sex of said medaka by the presence or absence of leucophores and/or a DNA marker, SL1 ... ." Office Action at page 9 (emphasis added). Because this language almost exactly recites the language of claim 5, the Office again acknowledges that claim 5 is enabled.

Further, Applicants respectfully submit that the Office implicitly recognizes that claim 6 is also enabled. Claim 6 is directed to a see-through medaka produced by means of further selective mating between the see-through medaka of claim 3 and the see-through medaka recited in claim 5. As the Office has found enablement with respect to both claims 3 and 5, it follows that the Office would accept that medaka produced by further selective mating between the medaka of those same two claims are also enabled.

With respect to claims 1 and 4, Applicants respectfully traverse the Office's rejections. According to the Office, the specification is enabling for a see-through medaka deficient in iridophores, melanophores, xanthophores and leucophores, where the deficiency results from repeated mating between specific medaka strains, but not where the deficiency is a result of any number and type of mutations in the genes involved in the pigmentation pathways of medaka. Office Action at pages 4, 5 and 6. Similarly, the Office contends that the specification is only enabling for a see-through medaka deficient in iridophores, melanophores, and xanthophores, whose sex is identified by the presence or absence of leucophores and/or a DNA marker, SL1, where the deficiency results from repeated mating between certain medaka strains. Office Action at pages 7, 8 and 9

However, Applicants should not be limited to the specific examples because the specification provides broad enablement for the production of the medaka of claims 1 and 4. For example, Example 1, on pages 12-17 of the Specification, provides at least two

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detailed examples for producing the medaka of claim 1. That is, the specification describes how the selected parental strains are mated in six and nine successive rounds to produce medaka deficient in iridophores, melanophores, xanthophores and leucophores. Specification, pages 14-16. Similarly, Example 2, on pages 17-27 of the Specification, provides at least four examples for producing the medaka of claim 4. This example includes information on how the parental strains are selected and used in three rounds of mating to produce see-through medaka where males are identified by the presence of leucophores and the presence of two bands of a DNA marker. Specification pages 17-22. Another two examples of see-through medaka within claim 4 are produced using medaka generated by crossed-over sex chromosomes of the above example for further rounds of mating. Specification pages 22-25. And a different crossing-over and round of mating yields yet another example of the medaka of claim 4. Specification at pages 26-27.

Indeed, a review of the *Wands'* factors demonstrate that the invention can be practiced without undue experimentation. M.P.E.P. § 2164.01(a); *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

(a) The Breath (or Scope) of the Claims

The Office contends that the breath of the claims 1 and 4 surpass that enabled by the specification. Office Action at pages 6 and 9. Rather than being overly broad, however, Applicants point out that claims 1 and 4 are directed to a specific fish, medaka. Indeed, in *Ex parte Chen*, 61 U.S.P.Q.2d 1025 (Bd. Pat. App. & Interf. 2000), the Board characterized claims to a transgenic carp as "narrow in being limited to a specific fish." *Id.* at 1027. The claims of the instant application are even further focused in that the

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claimed fish are also "see-through" and are deficient in iridophores, melanophores, xanthophores and leucophores.

Moreover, the instant case is quite unlike the typical nonenablement cases where claims are drawn to types of organisms not described in the working examples of the specification. See examples listed in M.P.E.P. § 2164.06(b), including *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 52 U.S.P.Q.2d 1129 (Fed. Cir. 1999) (working examples involved *E. coli,* while claims were directed to any cellular organism); *In re Wright*, 999 F.2d 1557, 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993) (working examples involved the Prague Avian Sarcoma Virus, while claims were directed to all RNA viruses; *In re Goodman*, 11 F.3d 1046, 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993) (working examples involved dicotyledonous plants, while claims were made to all plants). Unlike those cases, claims 1 and 4 are directed to the same type of organism as the one used in the working examples - medaka fish. Thus, the specification provides support commensurate with the breath of these claims, especially in terms of the type of organism claimed.

(b) The Nature of the Invention

In light of the nature of selective mating, Applicants remind the Office that some experimentation can be required, as long as it is not undue. *In re Vaeck*, 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991). In particular, the need for a repetitive procedure does not indicate "undue experimentation" by those wishing to practice the invention. *Chen*, 61 U.S.P.Q.2d at 1028. In *Wands*, for example, the Federal Circuit noted that the nature of monoclonal antibody technology is such that it involves screening hybridomas to determine the ones that make the desired antibody. *Wands*, 858 F.2d at 740, 8 U.S.P.Q.2d at 1406-07. Accordingly, this procedure did not amount to undue

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experimentation. *Id.* Similarly, here, practitioners of the art would be prepared to perform repeated selective mating to arrive at the claimed medaka. Indeed, medaka's short term for sexual maturation allows successive rounds of mating to be performed every two months. Specification at page 2, line 5. This short procedure cannot be deemed "undue experimentation" in the art of selective mating.

(c) The State of the Prior Art

As noted above, medaka is widely used as a simple and useful experimental animal. Specification at page 2. Indeed, Mendelian inheritance in fish was first confirmed in studies with medaka in the early 1900's, and many mutant strains have since been collected, studied and stably-maintained at universities. Ozato *et al. Developmental Genetics of Medaka*, Develop. Growth & Differ., Vol. 38, No. 5, pp 436-443 (1994), at page 437, right column, subsection on "Mutagenesis, Spontaneous Mutants," lines 1-10. In particular, the Office recognized the availability of color mutants, pertinent to the present invention. Office Action at pages 8-9. The Office further acknowledged that the most of them are recessive, un-linked mutations. Office Action at page 9. Because those in the field are familiar with the starting materials of the present invention, and thoroughly understand Mendelian inheritance of independent, recessive genes, it follows that one of skill in the art could fully practice the invention over the scope of its focused claims upon reading the detailed specification.

(d) The Level of One of Ordinary Skill

Applicants respectfully accept that the level of skill in this field is high. Indeed, the Office noted that "the skill of an artisan in this subject area is considered to be very high." Office Action at pages 6, 9 and 12. Consequently, it follows that such a skilled artisan, familiar with medaka, could practice the invention over the full scope of its claims.

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(e) The Level of Predictability in the Art

The Office contends that "it is unpredictable how these various color mutants would be inherited and what the resulting phenotype would be ... ." Office Action at pages 5-6 and 9. Yet, contrary to the Office's contention, the application need not teach "the specific genetic mutations" that result in the claimed medaka. Office Action at pages 5 and 8. As noted above, exact reproducibility is not a requirement of 35 U.S.C. § 112, first paragraph, where the claims neither include nor require that the genetic make-up of the organisms be the same. *Ex parte Chen*, 61 U.S.P.Q.2d 1025, 1028 (Bd. Pat. App. & Interf. 2000). Because the medaka of the instant claims need not be of identical genetic make-up, the Office's concern regarding predictability in this regard is inapposite.

Nevertheless, the predictability of successfully obtaining the claimed medaka is evidenced throughout the instant specification. All the mating data show that expected phenotypic and genotypic ratios were obtained for each of the rounds of mating. See Tables 2, 4, 6, 11, 13, 15, 17, 19, 21, and 23, on pages 14-38 of the Specification. As one of skill in the art would understand, these ratios indicate the proportion of progeny expressing the phenotype/genotype of interest for the given mating round. Further, a skilled artisan would recognize that they correlate with expected Mendelian ratios based on stable, independent inheritance of recessive mutant genes.

For example, in Table 2, mating between iridophore-deficient mutant medaka strain "gu" and albino mutant medaka strain "i-3" produces medaka heterozygous at two color mutant loci in the F1 generation (gu/+, i-3/+). And after a further round of mating, 1/16 of the F2 generation are homozygous recessive at both loci (gu/gu, i-3/i-3). Subsequent mating of these medaka with another color mutant medaka strain, "1f," produce medaka heterozygous at three color mutant loci in the F3 generation. These

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are crossed to obtain triply homozygous recessive mutants in 1/64 of the F4 generation, and so on, as indicated in Tables 2, 4, 6, 11, 13, 15, 17, 19, 21, and 23. Hence, rather than being unpredictable, the medaka of the claimed invention are obtained in accordance with elementary laws of Mendelian genetics. One of skill in the art could similarly predict the inheritance of other color mutations that are also recessive and unlinked. Thus, using other color mutant medaka as parental strains, and following mating schemes analogous to those presented, one of skill could reliably obtain the see-through medaka of claims 1 or 4, without undue experimentation.

(f) The Existence of Working Examples

The specification provides multiple working examples involving a variety of medaka strains. See Specification, pages 12-27, providing at least six working examples, described in detail above, for the medaka of claims 1 and 4. While cases involving physiological activity may require more guidance, "even in unpredictable arts, a disclosure of every operable species is not required." M.P.E.P. § 2164.03. That is, even in such cases, one need not necessarily disclose a working example for every embodiment encompassed by the claim. *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). Furthermore, while the instant invention entails biological activities, the specific genetics involved are long studied, well understood and evidently predictable, as discussed above. Thus, Applicants respectfully submit that the multiple embodiments described in the instant specification fully support claims 1 and 4 directed to specific medaka fish.

(g) The Amount of Direction Provided by the Inventor

The instant specification provides explicit instructions on how to conduct the repeated matings to obtain the medaka of claims 1 and 4. See, for example, Table 2 on

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page 14 and Table 4 on page 16 for claim 1, as well as Table 6 on page 19, Table 11 on page 23, Table 13 on page 25, and Table 15 on page 27 for claim 4. The tables detail the genotypes and phenotypes of the fish in descendent generations used in successive rounds of mating in order to arrive at the claimed organism. *Id.*

For example, as discussed at length above, Table 2 shows how the resulting genotypic and phenotypic ratios, through six rounds of mating, produce medaka deficient in iridophores, melanophores, xanthophores and leucophores. Specification, page 14. Likewise, Table 4 explains, at a genetic level, how five further rounds of mating produce another example of the medaka within claim 1. Specification, page 16. Similarly, Table 6 shows how the resulting phenotypes and genotypes of male and female progeny produce the medaka within claim 4 after three rounds of mating. Specification at page19. Table 10 explains the genotypes produced by crossing-over sex chromosomes of certain strains, and Tables 11 and 13 indicate how the resulting medaka produce two more examples of medaka within claim 4 in one and three further rounds of mating. Specification pages 23-25. Table 14 again explains the genotype produced by another crossing-over of sex chromosomes, and Table 15 indicates, in genetic detail, how this resulting medaka produces yet another example of claim 4 in one additional round of mating. Specification at pages 26-27.

Applicants submit that these detailed examples, providing phenotypic and genotypic mating data of the medaka, would guide a skilled artisan to practice the invention over the full scope of its claims.

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(h) The Quantity of Experimentation Needed to make or use the Invention based on the Content of the Disclosure

On reading the specification, one of skill in the art would have no difficulty in producing the claimed medaka. As noted previously, a skilled artisan would simply select color mutant medaka from stable, available strains, known to carry independent, recessive mutations. The artisan would then perform repeated rounds of mating, analogous to the ones detailed in the specification, based on well-established techniques for mating and breeding medaka. Simply selecting the clearest progeny of each generation for successive matings, he would successfully obtain the expected Mendelian ratios of the phenotype and genotype of interest. With each round taking approximately two months from mating to full sexual maturity of progeny, a skilled artisan could reliably produce any of the claimed medaka within a finite period. Indeed, this represents a small quantity of experimentation in the art of selective mating to obtain an animal with particular characteristics.

In light of the above factors, Applicants respectfully submit that the specification provides sufficient disclosure to enable one of skill in the art to make the medaka claimed in claims 1 and 4 without undue experimentation. Applicants thus earnestly request reconsideration and withdrawal of these rejections.

Finally, the Office rejected claims 7-22 as allegedly not being fully enabled by the specification. Office Action at page 10. The Office stated that "[t]he specification only teaches a transgenic see-through medaka wherein a specific organ is allowed to produce luminescence by introducing a hybrid gene being a fusion of an olvas gene promoter, which expresses specifically in the gonadal organ of said medaka, with a coding region of a gene encoding a green fluorescent protein." Office Action at pages 11 and 12.

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However, according to the Office, the specification does not disclose a variety of organ-specific promoters, nor a variety of hybrid genes operably linked to a variety of organ-specific promoters. Office Action at pages 11 and 12. Thus, the Office opined that it would require undue experimentation for a skilled artisan to practice the full scope of the claimed invention. Office Action at pages 12 and 14.

Applicants appreciate the Office's suggestion regarding the term "transgenic" and, solely to facilitate prosecution, have amended claims 7-22 accordingly. As noted above, the amendment is supported by the specification and adds no new matter. (See, for example, Specification at page 10, line 7 and line 26, and page 30, line 5).

Further, Applicants point out that the specification does provide examples of a variety of fluorescent protein genes and a variety of organs that can be selected. For example, the specification describes that such organs include "gonadal tissues (germ cells), brain, nerves, liver and muscles." Specification at page 9, lines 21-23. Similarly, the specification offers multiple examples of fluorescent protein genes, including "green fluorescent protein (... "GFP") gene of *Aequorea victoria*, blue fluorescent protein (BFP) gene and yellow fluorescent protein (YFP) gene," available from CLON TECH Inc. Specification page 9, lines 28-29 to page 10, lines 1-3.

Though the Office contended that the disclosure only teaches what is intended to be done, without teaching how to do it (Office Action at page 13), Applicants respectfully submit that "[s]imulated or predicted test results and prophetical examples (paper examples) are permitted in patent applications." M.P.E.P. § 608.01(p); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77, 224 U.S.P.Q. 409, 413-14 (Fed. Cir. 1984). This is especially true where the prophetic examples are based on actual experiments that are slightly modified and that would help someone make the

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invention. *Atlas Powder*, 750 F.2d at 1577, 224 U.S.P.Q. at 414. The examples of specific organs and fluorescent protein genes of the instant application present modified versions of the actual experiments performed involving gonadal expression of green fluorescent protein. Specification, pages 27-40. Also, the specification discloses where to obtain the various fluorescent protein genes, which would help someone make the invention. Thus, the specification provides support for more than just gonadal-specific expression of a gene encoding green fluorescent protein fused with an olvas gene promoter.

Furthermore, constructing a variety of hybrid genes with organ-specific promoters operably linked to the coding region of fluorescent protein genes involves standard methodologies known in the art of molecular biology. Indeed, other organ-specific promoters for medaka were known as of the priority date, and were used to create reporter constructs. Consider, for example, Kusakabe *et al.*, *In vivo analysis of two striated muscle actin promoters reveals combinations of multiple regulatory modules required for skeletal and cardiac muscle-specific gene expression*, Int. J. Dev. Biol., Vol. 43, pp 541-554 (1999); and Kinoshita *et al.*, *Activity of the medaka translation elongation factor 1α-A promoter examined using the GFP gene as a reporter*, Develop. Growth & Differ., Vol. 42, pp 469-478 (2000) (attached). These articles respectively describe creating hybrid genes using muscle-specific and non-muscle-specific promoters from medaka, operably linked to fluorescent reporter genes. Thus, using methods known in the art, one could readily construct different hybrid genes, fusing such organ-specific promoters to a known fluorescent protein gene, that could then be microinjected into medaka embryos. This straight-forward procedure indeed cannot be deemed undue experimentation.

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Additionally, organ-specific promoters for closely-related species were also well known as of the priority date, facilitating cloning of the corresponding medaka promoters by standard molecular biology techniques. Consider, for example, Long, *et al.*, *GATA-1 expression pattern can be recapitulated in living transgenic zebrafish using GFP reporter gene*, Development, Vol. 124, pp 4105-4111 (1997) (attached), which describes the expression of a zebrafish erythroid-specific promoter linked to a fluorescent reporter; and Higashijima, *et al.*, *Visualization of cranial motor neurons in live tansgenic zebrafish expressing green fluorescent protein under the control of the Islet-1 promoter/enhancer*, J. of Neurosci., Vol. 20, No. 1, pp 206-218 (Jan. 1, 2000) (attached), which discloses a zebrafish neuron-specific promoter. Using these known promoters to clone the corresponding regulatory elements in medaka, a skilled artisan could construct additional organ-specific constructs for use in the instant invention without undue experimentation.

Furthermore, Applicants respectfully submit that the Office's concerns regarding the stability of GFP are inapposite with respect to the instant invention. Office Action at page 13. As the Office notes, Linney et. al, Developmental Biology, Vol 213, No. 1 pp 207-216 (1999), point out a problem of GFP's stability in rapidly-developing systems. The problem involved early detection of fluorescence from *stable* GFP in the oocyte, masking that from the transgene in the zygote's genome. Linney, page 211, left column, lines 13-21 and right column, lines 31-40. However, Linney explains that this "problem" is transient, diminishing significantly in just 48 hours. Linney, page 211, right column lines 39-41. Hence, it would not affect the ability to ultimately obtain the transgenic medaka of claims 7-22.

Moreover, this "problem" reflects the *stability*, rather than the instability, of GFP-expression in fish systems. Such stability indicates that GFP expression should be

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readily obtained with other constructs, improving the predictability of different hybrid genes in transgenic fish. That is, the Linney reference attests to the stability and predictability of GFP expression in transgenic fish containing promoter-GFP constructs, contrary to the Office's construal that expression of different constructs would be unpredictable. Office Action at page 13. Furthermore, the art teaches that :

> "[T]ransgeinc techniques have been established in medaka. Foreign genes can be transferred and transmitted to the next generation and can exhibit controllable expression when expression vectors containing regulatory elements of medaka origin are used."

Ozato *et al. Developmental Genetics of Medaka*, Develop. Growth & Differ., Vol. 38, No. 5, pp 436-443 (1994), at page 441, left column, lines 1-6. Claims 7-22 involve expression vectors containing regulatory elements (promoters) that express in specific medaka organs. If these are of medaka origin, as in the case of the ovals gene promoter, such expression is known in the art to be controllable, transmissible and thus predictable. *Id.* Thus, this knowledge in the art further speaks to the predictability of how different constructs would affect transgenic expression in medaka.

Furthermore, more recent articles demonstrate the stability and predictability of different reporters in transgenic medaka. Consider, for example, Niwa, *et al.*, *Expression of GFP in nuclear transplants generated by transplantation of embryonic cell nuclei from GFP-transgenic fish into nonenucleated eggs of medaka, Oryzias latipes*, Cloning, Vol. 2, No. 1, pp 23-34 (attached). Niwa *et al.* describe the expression of a GFP-hybrid gene after transplantation into nonenucleated medaka oocytes. Importantly, the expression faithfully reflected the organ-specific property of the promoter used. See page 32, subheading "Faithful expression of the GFP gene in embryos and adult tissues in nuclear transplants." Similarly, Kinoshita, *et al.*, *supra*, describe tissue- and stage-specific

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expression of a GFP in transgenic medaka using the elongation factor-1α-A promoter. Notably, the transgene there was transmitted according to Mendelian law. See page 474, left column, lines 2-3. Thus, these articles further indicate that different constructs would be predictably expressed in the transgenic medaka of the instant invention.

In sum, based on the detailed guidance provided in the working examples on pages 27-40 of the specification, and the existence of additional examples on pages 9-10, along with the knowledge in the art, the predictability of results, and the focus of the claims, Applicants submit that any experimentation necessary to practice the invention over the full scope of claims 7-22 would not be undue and that the specification is enabling for claims 7-22.

For at least the above reasons, Applicants earnestly and respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph, rejections.

Claim Rejections under 35 U.S.C. § 102

The Examiner rejected claims 7-22 under 35 U.S.C. § 102(a) as allegedly anticipated by Tanaka *et al.* (Proceedings of the National Academy of Sciences, Vol. 98, No. 5, pp 2544-49, February 27, 2001). Office Action at page 14. Applicants respectfully traverse.

Applicants submit that the Tanaka reference is not prior art with respect to the instant application. Tanaka's publication date is February 27, 2001. The application claims priority to the Japanese Patent Application 2000-172375, filed on June 8, 2000, and Applicants have filed a certified priority document and an English language translation of its cover page. Thus, Applicants respectfully point out that June 8, 2000 is the effective filing date. M.P.E.P. § 706.02(b). Accordingly, the reference's date is not

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"before the invention thereof by the applicant," as required under 35 U.S.C. § 102(a), and thus cannot be prior art against the invention.

For at least this reason, Tanaka *et al.* cannot anticipate claims 7-22. Applicants thus respectfully request reconsideration and withdrawal of the § 102 rejections.

Conclusion

In view of the foregoing remarks, Applicants submit that all of the pending claims, as amended, are in condition for allowance. Thus, Applicants respectfully request timely issuance of a Notice of Allowance.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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By: Jean B. Fordis
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Dated: July 15, 2002

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APPENDIX

7. (Amended) [The] A transgenic see-through medaka [according to claim 1] deficient in iridophores, melanophores, xanthophores and leucophores, wherein a specific organ is allowed to produce luminescence by introducing a hybrid gene being a fusion of a promoter of a gene which expresses specifically in said organ, with a coding region of a gene encoding a fluorescent protein.

8. (Amended) [The] A transgenic see-through medaka [according to claim 3] produced by means of further selective mating between the see-through medaka according to claim 2 and iridophore deficient mutant medaka strain il-1, wherein a specific organ is allowed to produce luminescence by introducing a hybrid gene being a fusion of a promoter of a gene which expresses specifically in said organ, with a coding region of a gene encoding a fluorescent protein.

9. (Amended) [The] A transgenic see-through medaka [according to claim 4] deficient in iridophores, melanopores and xanthophores, wherein the sex of said medaka can be identified by the presence or absence of leucophores and/or a DNA marker, wherein a specific organ is allowed to produce luminescence by introducing a hybrid gene being a fusion of a promoter of a gene which expresses specifically in said organ, with a coding region of a gene encoding a fluorescent protein.

10. (Amended) [The] A transgenic see-through medaka [according to claim 6] produced by means of further selective mating between the see-through medaka according to claim 3 and a see-through medaka produced by means of repeated selective mating between iridophore deficient mutant medaka strain gu, albino mutant medaka strain i-3, leucophore deficient mutant medaka strain 1f, and medaka FLF strain which is deficient in leucophores in the female, wherein a specific organ is allowed to

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produce luminescence by introducing a hybrid gene being a fusion of a promoter of a gene which expresses specifically in said organ, with a coding region of a gene encoding a fluorescent protein.

11. (Amended) The transgenic see-through medaka according to claim 7 wherein said gene encoding the fluorescent protein is a gene encoding a green fluorescent protein.

12. (Amended) The transgenic see-through medaka according to claim 8 wherein said gene encoding the fluorescent protein is a gene encoding a green fluorescent protein.

13. (Amended) The transgenic see-through medaka according to claim 9 wherein said gene encoding the fluorescent protein is a gene encoding a green fluorescent protein.

14. (Amended) The transgenic see-through medaka according to claim 10 wherein said gene encoding the fluorescent protein is a gene encoding a green fluorescent protein.

15. (Amended) The transgenic see-through medaka according to claim 7 wherein said organ is a gonadal organ.

16. (Amended) The transgenic see-through medaka according to claim 8 wherein said organ is a gonadal organ.

17. (Amended) The transgenic see-through medaka according to claim 9 wherein said organ is a gonadal organ.

18. (Amended) The transgenic see-through medaka according to claim 10 wherein said organ is a gonadal organ.

19. (Amended) The transgenic see-through medaka according to claim 11 wherein said organ is a gonadal organ.

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20. (Amended) The transgenic see-through medaka according to claim 12 wherein said organ is a gonadal organ.

21. (Amended) The transgenic see-through medaka according to claim 13 wherein said organ is a gonadal organ.

22. (Amended) The transgenic see-through medaka according to claim 14 wherein said organ is a gonadal organ.

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